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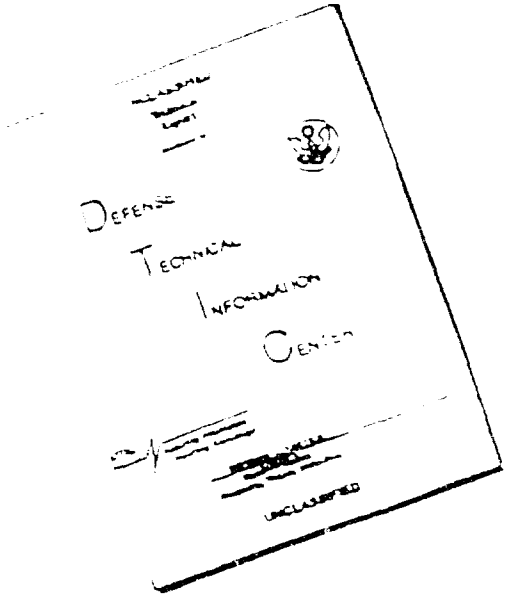

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US ARMY MEDICAL RESEARCH LABORATORY

FORT KNOX, KENTUCKY

REPORT NO. 551

EFFECT OF SALMONELLA TYPHOSA ENDOTOXIN ON RENAL FUNCTION, AND THE RELATIONSHIP OF FUNCTION TO RENAL HEMODYNAMICS

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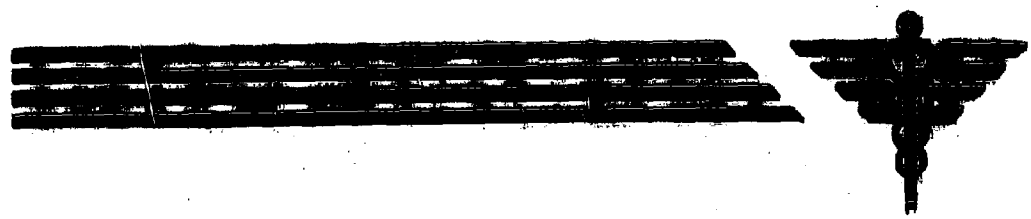

UNITED STATES ARMY
MEDICAL RESEARCH AND DEVELOPMENT COMMAND

13 September 1962

Report Submitted 9 August 1962

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AD Accession No.

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Report No. 551, 13 Sep 62. 20 pp & ii - 7 illus - 2 tables - Project No. 6X59-01-001, Unclassified Report

UNCLASSIFIED

1. Renal Function
2. Renal Hemodynamics
3. Endotoxin
4. *Salmonella typhosa*

Injection of endotoxin into the perfused left renal artery produced an immediate (18 sec) transient vasoconstriction followed by a severe renal vasoconstriction (5 to 10 min) and a decrease in all renal function. The delayed response was blocked by locally infused phentolamine. It is concluded that the delayed vasoconstriction is induced by a systemic release of catecholamine. In a group of animals the hemodynamic effect was eliminated in one kidney by infusing phentolamine locally and holding renal blood flow constant, enabling the comparison of this kidney with the contralateral undisturbed kidney. In the kidney in which vascular effects were eliminated there was no alteration in renal functions after systemic or local injection of endotoxin. These data show that the primary effect of endotoxin on the dog kidney is hemodynamic and not nephrotoxic.

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EFFECT OF SALMONELLA TYPHOSA ENDOTOXIN ON RENAL FUNCTION, AND THE RELATIONSHIP OF FUNCTION TO RENAL HEMODYNAMICS

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Fort Knox, Kentucky

13 September 1962

Radiation and Thermal Burns
Task 03
Surgery
USAMRL Project No. 6X59-01-001

Report No. 551
USAMRL Project No. 6X59-01-001-03

ABSTRACT

EFFECT OF SALMONELLA TYPHOSA ENDOTOXIN ON RENAL FUNCTION, AND THE RELATIONSHIP OF FUNCTION TO RENAL HEMODYNAMICS

OBJECT

This study was designed to determine whether the decrease in renal function seen after endotoxin administration is hemodynamic or due to nephrotoxicity of endotoxin.

RESULTS

The injection of endotoxin locally or systemically caused intense renal vasoconstriction and decrease in all renal functions. Locally infused phentolamine blocked the vasoconstriction and the renal function remained normal after endotoxin injection.

CONCLUSIONS

These studies demonstrate that after injection of endotoxin there is intense renal vasoconstriction which is apparently due to systemic release of catecholamine. The alterations in renal function are due to changes in renal hemodynamics and not nephrotoxicity.

RECOMMENDATIONS

Since the preparation utilized was found to be stabile and the vascular responses predictable, this may provide a reliable bio-assay for microwave-irradiated endotoxin.

ACKNOWLEDGEMENT

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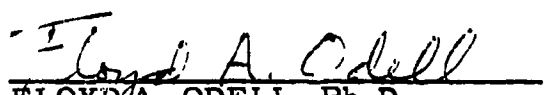
APPROVED: 

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EFFECT OF SALMONELLA TYPHOSA ENDOTOXIN ON RENAL FUNCTION, AND THE RELATIONSHIP OF FUNCTION TO RENAL HEMODYNAMICS

I. INTRODUCTION

Impaired renal function due to endotoxin has been reported in humans (1, 2) and experimental animals (3, 4). The altered renal function has been attributed to intense renal vasoconstriction and a fall in renal perfusion pressure. The vasoconstriction has been postulated to be due to both a direct local action of endotoxin on the renal vascular bed and to secondary systemic release of vasoconstrictor agents during the systemic hypotension (3). In an attempt to separate the hemodynamic from a possible nephrotoxic action of endotoxin, the local effects of Salmonella typhosa endotoxin were observed simultaneously in the dog kidney perfused at a constant blood flow and in the contralateral undisturbed kidney perfused naturally. The results of these studies are the subject of this report.

II. METHOD

Perfusion Procedures. Dogs, weighing 10 to 15 kg, were anesthetized with intravenous sodium pentobarbital (33 mg/kg). Heparin sodium (6 gm/kg) was administered intravenously. The kidney was perfused by the technique of Hardin et al (5). In brief, the abdominal aorta was exposed retroperitoneally through a left flank incision and the lumbar vessels tied. Blood was then withdrawn from a carotid artery by a precalibrated, pressure-independent Sigmamotor pump (Model T-6) and perfused into the abdominal aorta in a cephalad direction through a right angle glass cannula tied in position 3 cm below the left renal artery. Taking care not to disturb the left kidney, the aorta was occluded with a Potts clamp placed between the left and right renal arteries. This diverted the entire output of the pump through the left kidney. Renal blood flow was adjusted to an average value of 150 ml/min (range 95 to 220 ml/min) which produced a mean arterial perfusion pressure of approximately 100 mm Hg. This provided a blood flow of approximately 3.0 ml/gm of kidney tissue.

Renal arterial, renal venous, and systemic arterial pressures were measured by a needle inserted in the perfusion tubing just proximal to the glass cannula, by directly needling the renal vein, and by needling the proximal aorta, respectively. Pressures were recorded on a direct writing oscillograph recorder connected to Statham pressure transducers. Renal vascular resistances were calculated by dividing the pressure gradient from renal artery to renal vein by the blood flow and expressed as mm Hg/ml/min.

Endotoxin. Lethal doses (0.6 mg/kg) of Salmonella typhosa 0901 endotoxin (Bacto lipopolysaccharide, Difco Laboratories) were injected in one bolus directly into either the perfusion system just proximal to the renal artery (15 dogs) or systemically into the inferior vena cava (8 dogs). Renal vascular and systemic pressures were recorded for at least 10 minutes previous to and for 30 minutes following injection of endotoxin. Five additional animals were observed over a 30 minute period to obtain technique control values.

Contribution of Catecholamines. The contribution of catecholamines was delineated by the continuous infusion of phentolamine methanesolfonate (5-10 μgm/min) directly into the renal perfusion circuit. This amount of phentolamine has been shown by others (6, 7) to be of sufficient concentration to block the local catecholamine effect without depressing systemic arterial pressure. After the phentolamine had been infused and renal and systemic vascular pressures remained stable, endotoxin was injected directly into the renal artery. Pressures were recorded over the following 30 minutes.

The tissue catecholamine levels were diminished in another group of dogs by pretreatment for three days with reserpine (8) (0.13 mg/kg intraperitoneally daily). On the fourth day endotoxin was administered locally into the renal artery and pressures recorded as described above.

Renal Function. Differential renal function was measured by comparing several renal functions of the undisturbed right kidney with the phentolaminized, perfused, left kidney. Urine was collected separately from each kidney by inserting polyethylene tubing retrograde into both ureters through a suprapubic incision. Three 10 minute control samples were obtained prior to the systemic administration (inferior vena cava) of endotoxin. Glomerular filtration rate (creatinine clearance), maximal tubular resorption of p-aminohippuric acid (TmPAH), sodium excretion ($U_{Na}V$), potassium excretion (U_KV), osmolal clearance (C_{OSM}), and free water clearance (C_{H_2O}) were obtained from each kidney for six 10 minute collection periods following systemic injection of endotoxin. Blood levels of creatinine (16-20 mg%) and of PAH (45-50 mg%) were maintained in all experiments and adequate urine flow (greater than 2 ml/min) was insured by mannitol diuresis. PAH was determined by the method of Smith et al (9), and creatinine by the method of Bonsnes and Taussky (10). Na and K were determined on a Coleman flame photometer. Osmolalities were determined on a Fiske osmometer. Osmolal clearance (C_{OSM}) equals urine osmolality (U_{OSM}) times the urine volume (V) (ml/min) divided

by plasma osmolality (P_{OSM}). $T^C_{H_2O} = C_{OSM} - V$ and represents the quantity of water that must be added to a minute volume of urine to dilute it to the concentration of plasma.

The division of animals in the different experiments is outlined in Table I. To eliminate the possible effects of pentobarbital anesthesia, morphine sulfate (15 mg) and chloralose (75 mg/kg) anesthesia were administered in one half of the animals in the renal function group.

The responses of local and systemic administration were compared by testing them statistically according to the student "t" test (11).

III. RESULTS

Initial Transient Vasoconstriction. As shown by the recording of a representative experiment in Figure 1, subsequent to injection of endotoxin into the perfused left renal artery, there was an immediate (18 sec) transient vasoconstriction followed by a secondary prolonged renal vasoconstriction (5 to 10 min). Both local and systemic injection of endotoxin caused this immediate transient vasoconstriction (Fig. 2) which persisted for 30-40 seconds. This increase in renal vascular resistance peaked at 18 seconds (average) after local injection and 28 seconds after systemic injection. Control injections of isotonic saline and pyrogen-free distilled water were without effect. The reserpinized animals and the dogs receiving the local infusion of phentolamine responded with similar transient increases in vascular resistances (Fig. 2).

Renal Artery Administration. There was a marked secondary prolonged renal vasoconstriction in all the dogs (Fig. 3) after the local administration of endotoxin into the renal artery. Although there was some variation in the intensity of the response, the maximum renal vasoconstriction was found between 5 and 10 minutes after the endotoxin injection and seemed to coincide with the drop in systemic pressure (Fig. 1). At 5 minutes the average renal arterial pressure had doubled and was maintained at this level for another 5 minutes (Fig. 4A). At 30 minutes the pressure had returned halfway to pre-injection levels. The renal venous pressure was increased by 90 per cent at 5 minutes and declined to an average of 20 per cent above the pre-endotoxin pressures at 30 minutes. Systemic pressure dropped maximally at 10 minutes (20 per cent), with an average 10 per cent below pre-injection pressures at the end of 30 minutes

(Fig. 4B). No significant changes were observed in renal artery, renal vein, or systemic arterial pressure of the five technique control dogs (Fig. 4).

Systemic Administration. The local administration caused an earlier and more intense secondary renal vasoconstriction than did the injection of endotoxin into the inferior vena cava. The comparison of the average renal and systemic arterial responses to endotoxin given by two different routes is shown in Figure 4. Local injection produced a 100 per cent increase in renal artery pressure at 5 minutes as compared to a 78 per cent increase if endotoxin was given systemically. The difference in renal arterial pressure at 5 minutes after local and systemic administration was statistically significant ($p < 0.01$). At 30 minutes there was a 40 per cent average increase in renal artery pressure after arterial injection, while intravenous endotoxin caused a 35 per cent increase. Systemic pressure declined in both experiments, but there was a greater decline in the systemic pressure after the local injection at the 5 and 10 minute interval which was barely statistically significant ($p = 0.05$).

Contribution of Catecholamines. In the five animals in which phentolamine was administered locally there was no secondary increase in the renal artery perfusion pressure after the local injection of endotoxin (Figs. 5 and 6). At 30 minutes there was a 30 per cent decrease in pressure. Systemic arterial pressure remained unchanged during the first 10 minutes and then gradually fell to 20 per cent of preinjection levels at 30 minutes. In the five dogs pretreated with reserpine there was also an intense secondary renal vasoconstriction associated with the systemic arterial hypotension (Fig. 5).

Differential Renal Functions. Table II and Figure 7 show the results of the renal functions measured in the perfused phentolaminized left kidney as compared with the undisturbed right kidney for each of the eight animals. Following systemic administration of endotoxin there was a progressive decrease in function of the right kidney in all eight animals. The average urinary output decreased from 4.4 ml/min to 1.2 ml/min and glomerular filtration rate decreased from 20 ml/min to 7.6 ml/min. The TmPAH decreased from 7.3 mg/min to 1.3 mg/min; $U_{Na}V$ decreased from 156 μEq/min to 22 μEq/min, the U_KV declined from 39 μEq/min to 6 μEq/min; C_{OSM} decreased from 5.3 ml/min to 1.9 mg/min; and the $T^c_{H_2O}$ decreased from 0.9 ml/min to 0.2 ml/min.

The phentolaminized left kidney, perfused at a constant rate, did not demonstrate the decreased renal functions measured in the naturally

perfused right kidney. The average urine volume increased from 2.4 ml/min to 3.9 ml/min, GFR 11.6 ml/min to 12.4 ml/min, $^{T}Na\,V$ 54 μEq/min to 126 μEq/min, and C_{OSM} 2.7 ml/min to 4.1 ml/min. There was a slight decline in TmPAH from 4.8 ml/min to 4.1 ml/min, $U_K V$ 30 μEq/min to 28 μEq/min, and $T^C_{H_2O}$ from 0.5 ml/min to 0.3 ml/min. The serum potassium levels decreased in all animals during the hour in which they were observed, while the plasma sodium remained unchanged.

IV. DISCUSSION

These data demonstrate that administration of lethal doses of Salmonella typhosa endotoxin directly into the renal artery produced intense renal vasoconstriction with consequent impairment of renal function.

Hinshaw and Bradley suggested that endotoxin had an initial direct effect on the renal vasculature followed by a secondary vasoconstriction at 10 minutes (3, 4), on the basis of a sudden fall in kidney weight, 15 to 35 seconds after endotoxin administration, followed by a minimum weight within 10 to 20 minutes. The pressure findings reported herein confirm and extend this impression of Hinshaw et al of the initial vasoconstriction followed by the secondary intense pressor phase at 10 minutes. The prompt vasoconstriction observed at 18 seconds during these experiments and in Hinshaw's experiments suggests that either the endotoxin molecule itself is a renal vasoconstrictor, or that it causes an immediate, transient release of pressor substances from the blood elements or renal tissue. Although there is a significant release of serotonin into the platelet-free plasma in the rabbit 15 seconds after endotoxin injection (12) this finding was not confirmed by the same workers in the dog (13). The initial pressor response could not be duplicated by large doses of serotonin injected locally into the renal artery. Pretreatment with reserpine and local infusion of phentolamine did not abolish this initial transitory pressor phase observed during the first minute (Fig. 2). It, therefore, seems that this initial, transient pressor phenomenon may be produced by the endotoxin molecule itself; however, the rapid local release of a pressor agent cannot be ruled out. It is interesting to note that this finding was not observed in other vascular beds studied in this laboratory (6, 14).

The injection of endotoxin directly into the renal artery caused a significantly more intense secondary renal vasoconstriction at the 5 minute interval than was observed when the endotoxin was administered systemically (Fig. 3A). This difference could be attributed to a

direct effect of endotoxin altering the reactivity of blood vessels to epinephrine (15-19). In addition, the concentration of endotoxin reaching the renal vascular bed could have been decreased by several factors, including systemic hemodilution as well as detoxification in the liver, lungs, and spleen after the systemic injection.

A detailed review of the hemodynamics of endotoxin shock found clinically and experimentally has been reported by Gilbert (20). Various studies have been reported on the effects of endotoxin on isolated, perfused vascular beds (6, 14, 21-23). Studies on the forelimb (24), lung (23), and gastric (6) circulations demonstrated vasoconstriction while the coronary vascular bed (14) responded by vasodilation. These responses have been and can be explained by a systemic release of pressor amines, since the effect of endotoxin on these vascular beds mimics the responses of epinephrine and norepinephrine (25-29). Evidence to support this concept is offered by the experiments with the phentolamine-treated kidneys. In these animals small doses of a phentolamine, administered locally into the perfused renal artery, prevented the renal vasoconstriction usually observed after endotoxin injection.

Further confirmation of this hypothesis may be offered by the data of the reserpine-treated dogs. Reserpine has been shown to diminish body stores of catecholamines (8). It has been demonstrated that blood vessels of reserpine-treated animals are hyper-responsive to these same catecholamines (30). These findings suggest that after the injection of the endotoxin, the remaining body catecholamines were liberated into the systemic circulation. The greater vasoconstriction observed during the first 5 minutes in reserpine-treated dogs could have been produced by an exaggerated vascular response of catecholamine-depleted renal vasculature. Then, as suggested by Burn and Rand (30) when norepinephrine was repleted in the renal vasculature, the constrictor response was similar to those animals not treated by reserpine.

There was no significant change in plasma sodium during the experiment. In contrast, serum potassium levels decreased markedly (Table II) after endotoxin administration. Since there was no increase in urinary excretion of potassium, it must have moved intracellularly. We have no explanation for this apparent shift of potassium intracellularly.

Hinshaw et al (4) showed that lethal doses of E. coli endotoxin produced a decreased RBF, GFR, PAH extraction, and urinary output.

These effects were attributed to the effects of systemic hypotension, renal vasoconstriction, and a possible nephrotoxic action. As they suggested, it was impossible from their study to measure changes in renal vascular pressures, and there was the further disadvantages of evaluating renal function in the presence of low urine flow rates. The present investigation was designed to measure changes in renal vascular pressures at a controlled, constant renal blood flow. Furthermore, in the renal function studies, adequate initial urine volumes were insured by osmotic diuresis, and the vascular effects were eliminated by local vascular blockage of catecholamine effects. In addition, this enabled comparison of the renal functions of one kidney not vasoconstricted with the other kidney exposed to all the local and systemic variables.

The undisturbed right kidney demonstrated similar decreases in kidney functions as were described by Hinshaw et al (4). There was a marked decrease in all of the measured functions. The average urine volume of all eight animals decreased by 75 per cent, TmPAH decreased 80 per cent, and GFR decreased by 60 per cent. The left kidney, which was maintained at a constant blood flow, and relatively unchanged pressure, demonstrated no significant decrease in any of the measured renal functions after the endotoxin injection. The observed increase in urine flow of the left kidney may be explained either by a possible diuretic action of phentolamine or by its action of vasodilation. This explanation is supported by the slight increase in GFR and the doubled sodium output of the left kidney during the phentolamine infusion.

In the renal function experiments, the only difference was that the vascular effect of catecholamines was eliminated in the left kidney; since endotoxin was administered systemically both kidneys should have received equal doses of endotoxin. In one animal (Dog No. 6), endotoxin was inadvertently given directly into the left renal artery. In this animal there was still no nephrotoxic effect demonstrated. The data, therefore, show that the primary effect of endotoxin on the kidney is hemodynamic and not nephrotoxic.

V. SUMMARY AND CONCLUSIONS

The injection of lethal doses of Salmonella typhosa endotoxin in the dog produced an initial (18 sec) transient vasoconstriction followed by a secondary intense vasoconstriction within 5 to 10 minutes after the injection. Renal arterial pressure remained elevated for 30 minutes. Since the local infusion of phentolamine blocked the secondary renal vasoconstriction it is suggested that the persistent vasoconstriction

is due to catecholamine release during the systemic hypotension. After endotoxin injection there is a marked decrease in all renal functions. In a group of animals the hemodynamic effect was eliminated in one kidney by infusing phentolamine locally and holding renal blood flow constant, enabling comparison of this kidney with the contralateral and undisturbed kidney. In the kidney in which vascular effects were eliminated there was no alteration in renal functions after systemic or local endotoxin injection. These data, therefore, show that the primary effect of endotoxin on the kidney is hemodynamic and not nephrotoxic.

VI. REFERENCES

1. Brande, A. J., J. Siemienski, D. Williams, and J. P. Sanford. Overwhelming bacteremic shock produced by gram-negative bacteria, a report of four cases with one recovery. Univer. Michigan M. Bull. 19: 23, 1953.

2. Brande, A. J., D. Williams, J. Siemienski, and R. Murphy. Shock-like state due to transfusion of blood contaminated with gram-negative Bacilli. A. M. A. Arch. Int. Med. 92: 75, 1953.

3. Hinshaw, L. B. and G. M. Bealey. Alterations in kidney weight produced by Escherichia coli endotoxin. Am. J. Physiol. 189: 329, 1957.

4. Hinshaw, L. B., W. W. Spink, J. A. Vick, E. Mallet, and J. Finstad. Effect of endotoxin on kidney function and renal hemodynamics in the dog. Am. J. Physiol. 201 (1): 144, 1961.

5. Hardin, R. A., J. B. Scott, and F. J. Haddy. Relationship of pressure to blood flow in the dog kidney. Am. J. Physiol. 199: 1192, 1960.

6. Dooley, E. S., J. B. Scott, E. D. Frohlich, and E. D. Jacobson. Hemodynamics of the stomach. III. Effects of Salmonella typhosa endotoxin on the resistance to blood flow. USAMRL Report No. 509, Ft Knox, Ky., 1961.

7. Haddy, F. J., J. B. Scott, M. Fleishman, and D. Emanuel. Effect of change in flow rate upon renal vascular resistance. Am. J. Physiol. 195: 111, 1958.

8. Waud, D. R., S. R. Kottegoda, and O. Krayer. Threshold dose and time course of norepinephrine depletion of the mammalian heart by reserpine. J. Pharmacol. and Exper. Therap. 124: 340, 1958.

9. Smith, H. W., N. Finkelstein, L. Aliminosa, B. Crawford, and M. Graver. The renal clearance of substituted hippuric acid derivatives and other aromatic acids in dog and man. J. Clin. Invest. 24: 388, 1945.

10. Bosnes, R. W. and H. H. Taussky. On the colorimetric determination of creatinine by the Jaffe reaction. J. Biol. Chem. 158: 581, 1945.

11. "Student." The probable error of a mean. Biometrika, 6: 1, 1908.

12. Davies, R. B., W. R. Meeker, and W. L. Bailey. Serotonin release by bacterial endotoxin. Proc. Soc. Exper. Biol. and Med. 108: 774, 1961.

13. Davies, R. B., W. R. Meeker, and D. G. McQuarrie. Immediate effects of intravenous endotoxin on serotonin concentration and blood platelets. Circulation Res. 8: 234, 1960.

14. Frohlich, E. D., J. B. Scott, and E. S. Dooley. Hemodynamic alterations due to Salmonella typhosa endotoxin with special reference to the coronary vascular bed. J. Clin. Invest. 41: 147, 1962.

15. Zweifach, B. W., A. L. Nagler, and L. Thomas. The role of epinephrine in reaction produced by endotoxin of gram negative bacteria. J. Exper. Med. 104: 881, 1956.

16. Thomas, L., B. W. Zweifach, and B. Benacerraf. The role of epinephrine in reaction produced by endotoxin of gram negative bacteria. J. Exper. Med. 104: 865, 1956.

17. Landy, M. and M. J. Shear. Similarity of host response elicited by polysaccharides of animal and plant origin and by bacterial endotoxins. J. Exper. Med. 106: 77, 1957.

18. Zweifach, B. W. and L. Thomas. The relationship between the vascular manifestations of shock produced by endotoxin, trauma, and hemorrhage. J. Exper. Med. 106: 385, 1957.

19. Thomas, L., B. W. Zweifach, and B. Benacerraf. Mechanisms in the production of tissue damage and shock by endotoxin. Tr. A. Am. Physicians, 70: 84, 1957.

20. Gilbert, R. P. Mechanism of the hemodynamic effects of endotoxin. Physiol. Rev. 40: 245, 1960.

21. Gilbert, R. P. and P. J. Gordon. Peripheral vascular reactions in experimental shock due to endotoxin. Clin. Res. Proc. 4: 110, 1956.

22. Mac Lean, U. D., M. H. Weil, W. W. Spink, and M. B. Visscher. Canine intestinal and liver weight changes induced by E. coli endotoxin. Proc. Soc. Exper. Biol. and Med. 92: 602, 1956.

23. Kuida, H., L. B. Hinshaw, R. P. Gilbert, and M. B. Visscher. Effect of gram-negative endotoxin on pulmonary circulation. Am. J. Physiol. 192: 335, 1958.

24. Hinshaw, L. B., J. A. Vick, M. M. Jordan, and L. E. Wittmers. Vascular changes associated with development of irreversible endotoxin shock. Am. J. Physiol. 202: 103, 1962.

25. Haddy, F. J., M. Fleishman, and D. A. Emanuel. Effect of epinephrine, norepinephrine and serotonin upon systemic, small, and large vessel resistance. Circulation Res. 5: 247, 1957.

26. Aviado, D. M., Jr. and C. F. Schmidt. Effects of sympathomimetics drugs on pulmonary circulation; with special reference to a new pulmonary vasodilator. J. Pharmacol. and Exper. Therap. 120: 512, 1957.

27. Jacobson, E. D. Effect of histamine, norepinephrine, and acetylcholine on gastric vascular resistance. The Physiologist (in press).

28. Berne, R. M. Effects of epinephrine and norepinephrine on coronary circulation. Circulation Res. 6: 644, 1958.

29. Hardin, R. A., J. B. Scott, and F. J. Haddy. Effect of epinephrine and norepinephrine on coronary vascular resistance in dogs. Am. J. Physiol. 201: 276, 1961.

30. Burn, J. H. and M. J. Rand. Noradrenalin in artery walls and its dispersal by reserpine. Brit. M. J. 1: 903, 1958.

TABLE I

Experimental design

A.	Renal artery administration:	
	1. Effect of local injection.	15 dogs
	2. Local injection with phentolamine infusion.	5 dogs
	3. Local injection in reserpinized animals.	5 dogs
B.	Inferior vena cava administration:	
	1. Effect of systemic injection.	8 dogs
	2. Renal function studies.	8 dogs
	(a) Pentobarbital anesthesia	4 dogs
	(b) Morphine and chloralose anesthesia	4 dogs
C.	Technique controls.	5 dogs

TABLE II

Effect of Salmonella typhosa endotoxin on renal function

Dog no.	Time min.	Syst. BP	L. RA Press.	Urine vol. L	Urine vol. R	GFR L	GFR R	TmPAH L	TmPAH R	C_{OSM} L	C_{OSM} R	$T^c_{H_2O}$ L	$T^c_{H_2O}$ R	$U_{NA}V$ L	$U_{NA}V$ R	U_KV L	U_KV R	Blood Na	Blood K
		mm/Hg	mm/Hg	ml/min		ml/min		mg/min		ml/min		ml/min		μEq/min		μEq/min		mEq/L	
	Control*	160	80	1.7	4.6	9.2	23.0	4.0	6.2	2.1	5.6	0.4	1.0	6	65	21	10	140	3.6
	0-10	155	95	0.7	3.7		14.6		5.3		4.2		0.5	2	38	6	7	139	3.2
1	10-20	135	95	1.7	3.1	6.4	12.2	3.8	5.0	1.8	3.5	0.1	0.4	20	21	14	7		
	20-30	120	105	1.8	2.4	7.2	10.1	3.0	4.9	2.0		0.2		22	12	13	5	139	2.6
	30-40	110	110	2.1	1.6	9.1	8.5	3.3	3.9	2.3	2.7	0.2	1.1	39	10	15	2	142	2.6
	Control*	165	140	1.4	3.8	8.9	21.6	7.1	11.9		4.9		1.1	140	122	17	22	141	2.8
	0-10	160	155	1.8	4.1	10.8	19.9				5.0		0.9	36	165	13	16	144	2.4
	10-20	155	130	1.9	4.0	9.4	16.8	5.7	8.9		4.8		0.8	40	132	10	13	139	2.2
2	20-30	115	90	2.1	3.1	7.2	11.8	6.5	1.8		3.7		0.6	54	100	9	9	140	2.0
	30-40	100	80	2.8	2.2	12.3					3.6		1.4	96	43	10	8	138	1.9
	40-50	100	80	2.9	1.6	15.2	8.5	5.4	-0.5		2.1		0.5	114	23	10	7	140	1.9
	50-60	75	75	4.3	1.2	15.8	6.7		-2.7		1.6		0.4	209	13	11	4	143	1.9
	Control*	125	70	2.0	5.7	11.1	21.9			2.3	6.2	0.3	0.5	26	230	17	42	141	3.8
	0-10	120	77	1.8	1.7	9.3	9.2			1.9	1.9	0.1	0.2	26	27	17	20	141	4.2
	10-20	110	80	2.2	2.2	12.2	13.7			2.3	2.6	0.1	0.3	24	20	19	30	143	3.8
3	20-30	90	85	2.5	2.6	10.8	12.9			2.6	2.7	0.1	0.1	39	27	20	19	145	3.1
	30-40	80	85	3.1	2.9	11.3	13.4			3.1	3.1	0.0	0.2	75	40	21	20	140	3.0
	40-50	90	90	3.5	2.8	12.5	12.9			3.3	2.9	+0.2	0.1	114	35	17	19	143	3.0
	50-60	55	90	3.6	2.7	13.3	13.8			3.2	2.9	+0.4	0.2	133	29	15	16	138	2.6
	Control*	150	92	2.5	2.8	14.0	19.7	4.2	3.8	3.1	3.9	0.6	1.1	19	51	35	42	142	3.4
	0-10	140	82	2.6	2.9	15.6	15.3	4.5	2.1	3.1	3.4	0.5	0.5	22	29	33	32	140	3.2
	10-20	127	82	2.4	2.4	12.8	10.5	2.9	2.7	2.7	2.8	0.3	0.4	17	24	30	30	140	3.3
4	20-30	122	82	2.4	1.9	11.0	9.0	3.6	2.7	2.7	2.6	0.3	0.7	16	19	30	28	132	3.1
	30-40	92	87	2.6	1.5	11.8	8.7	3.0	2.8	2.9	2.3	0.3	0.8	19	15	28	23	139	2.9
	40-50	82	92	2.6	0.9	13.2	8.1	4.0	1.9	2.9	1.7	0.3	0.8	22	9	27	16	137	2.6
	50-60	67	90	2.5	0.6	11.0	5.0	4.0	2.4	2.8	1.2	0.3	0.6	24	6	25	11	137	2.2
	Control*	137	90	3.0	5.7	14.7	19.4	3.8	7.0	3.9	7.1	0.9	1.4	111	423	28	55	140	3.8
	0-10	125	107	3.4	5.2	11.5	18.5	3.0	5.5	3.9	6.1	0.5	0.9	159	266	31	49	144	4.0
	10-20	105	105	4.0	4.9	12.9	15.6	3.3	5.6	4.4	5.5	0.4	0.6	189	230	28	45	143	3.5
5	20-30	100	102	3.9	4.4	16.1	15.8	3.6	4.2	4.2	5.0	0.3	0.6	191	194	17	35	147	3.2
	30-40	87	102	4.0	4.0	14.0	16.5	2.2	2.1	4.3	4.6	0.3	0.6	205	165	17	17	147	2.7
	40-50	77	107	4.2	3.6	12.8	13.2	2.9	-4.1	4.3	4.1	0.1	0.5	220	132	15	15	147	2.6
	50-60	62	100	4.8	2.7	12.8	11.6	2.9		4.8	3.2	0.0	0.5	276	74	14	10	150	2.4
	Control*	112	95	3.7	3.8	12.9	19.6	7.0	9.1	3.2	4.3	0.5	0.7	41	43	56	79	136	5.0
	0-10	100	97	3.2	3.1	14.5	14.6	10.2	6.5	3.6	3.4	0.4	0.3	26	41	64	63	138	4.6
	10-20	77	112	3.0	3.2	15.9	11.3	10.9	7.3	3.5	2.3	0.5	0.1	9	44	59	33	138	3.2
6	20-30	60	102	4.1	1.6	15.7	9.2	9.0	5.6	4.9	1.6	0.8	0.0	11	37	84	16	139	3.2
	30-40	50	107	4.5	1.0	18.2	6.2	11.6	4.9	5.6	1.0	1.1	0.0	14	25	88	7	141	2.9
	40-50	47	122	4.6	1.0	15.6	6.3	8.3	2.9	5.6	0.9	1.0	+0.1	18	28	103	6	141	2.4
	50-60	38	117	4.9	0.7	15.6	4.9	9.9	5.9	6.0	0.6	1.1	+0.1	15	21	106	3	141	2.4
	Control*	175	112	2.8	6.1	12.9	21.5	3.7	5.1	3.2	6.5	0.4	0.4	67	271	39	54	132	3.2
	0-10	165	102	3.1	4.8	12.4	16.4	3.2	4.0	3.4	5.1	0.3	0.3	65	169	33	43	131	2.9
	10-20	150	90	3.3	5.0	12.9	18.3	3.5	6.2	3.4	5.2	0.1	0.2	86	173	25	39	130	2.4
7	20-30	138	97	3.7	4.9	14.6	17.6	4.6	5.1	4.0	5.2	0.3	0.3	125	176	31	33	130	2.3
	30-40	125	100	3.7	3.9	12.1	14.0		3.8	3.8	4.1	0.1	0.2	139	120	17	17	129	2.2
	40-50	110	105	3.7	1.1	11.0	7.5	2.3	0.9	3.7	1.9	0.0	0.2	177	25	19	8	129	2.2
	50-60	97	100	3.7	0.6	9.3	3.3	2.8	-0.2	3.7		0.0		194	2	24		128	2.0
	Control*	160	135	1.7	3.9	8.8	14.6	4.1	4.6	1.9	3.6	0.2	0.7	18	45	29	12	148	4.0
	0-10	110	150	1.9	1.4	8.2	6.9	3.9	1.9	2.1	1.8	0.2	0.4	62	15	18	5	147	3.4
	10-20	122	127	2.5	0.5	9.9	3.5	5.8	1.4	2.8		0.3		72		28		147	2.7
8	20-30	115	132	2.6	0.7	10.7	3.8	4.6	2.2	2.8		0.2		73		16		147	2.5
	30-40	87	130	2.9	0.4	10.2	2.0	4.1	1.5	3.1		0.2		87		16		150	2.3
	40-50	72	140	3.2	0.1	12.8		5.1		3.4		0.2		102		18		144	2.3
	50-60	67	138	3.6	0.4	9.3		5.1		3.7		0.1		121		17		148	2.3

*Average of three 10-minute samples.

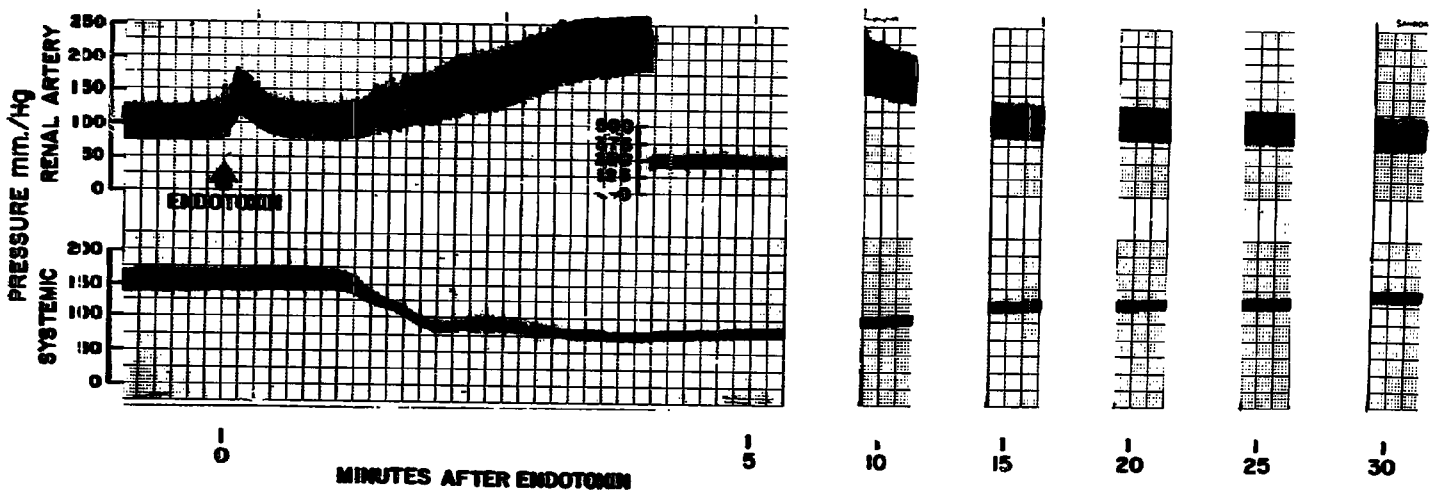

Fig. 1. A representative experiment in which endotoxin was injected directly into the renal artery. Note the initial transient vasoconstriction was followed by an intense renal vasoconstriction at 5 to 10 minutes.

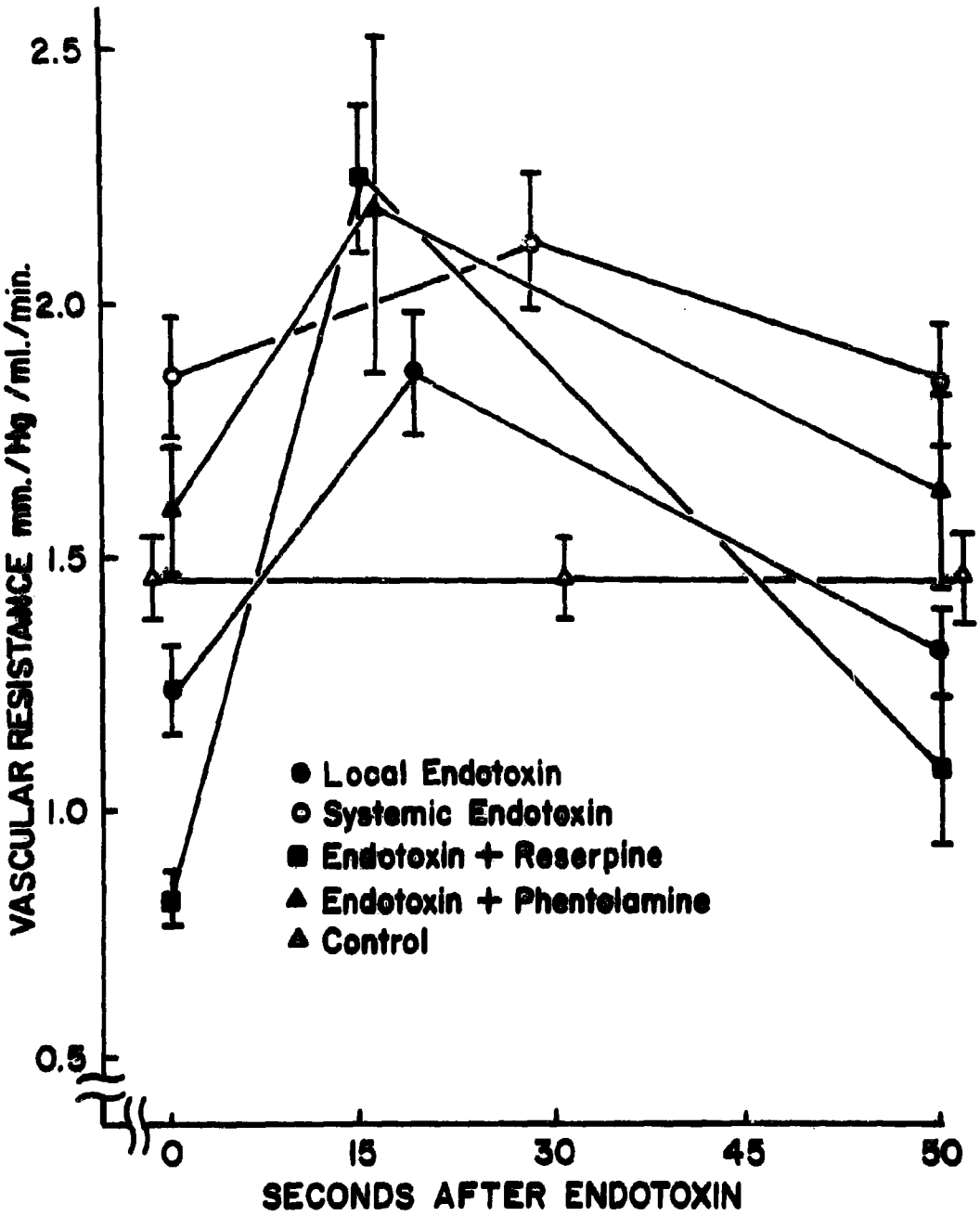

Fig. 2. Average increase in renal vascular resistance during the immediate transient vasoconstriction observed in the animals given endotoxin locally (15 dogs), systemically (8 dogs), pretreated with reserpine (5 dogs), and during the local infusion of phentolamine (5 dogs). ± 1 S.E.M. is indicated.

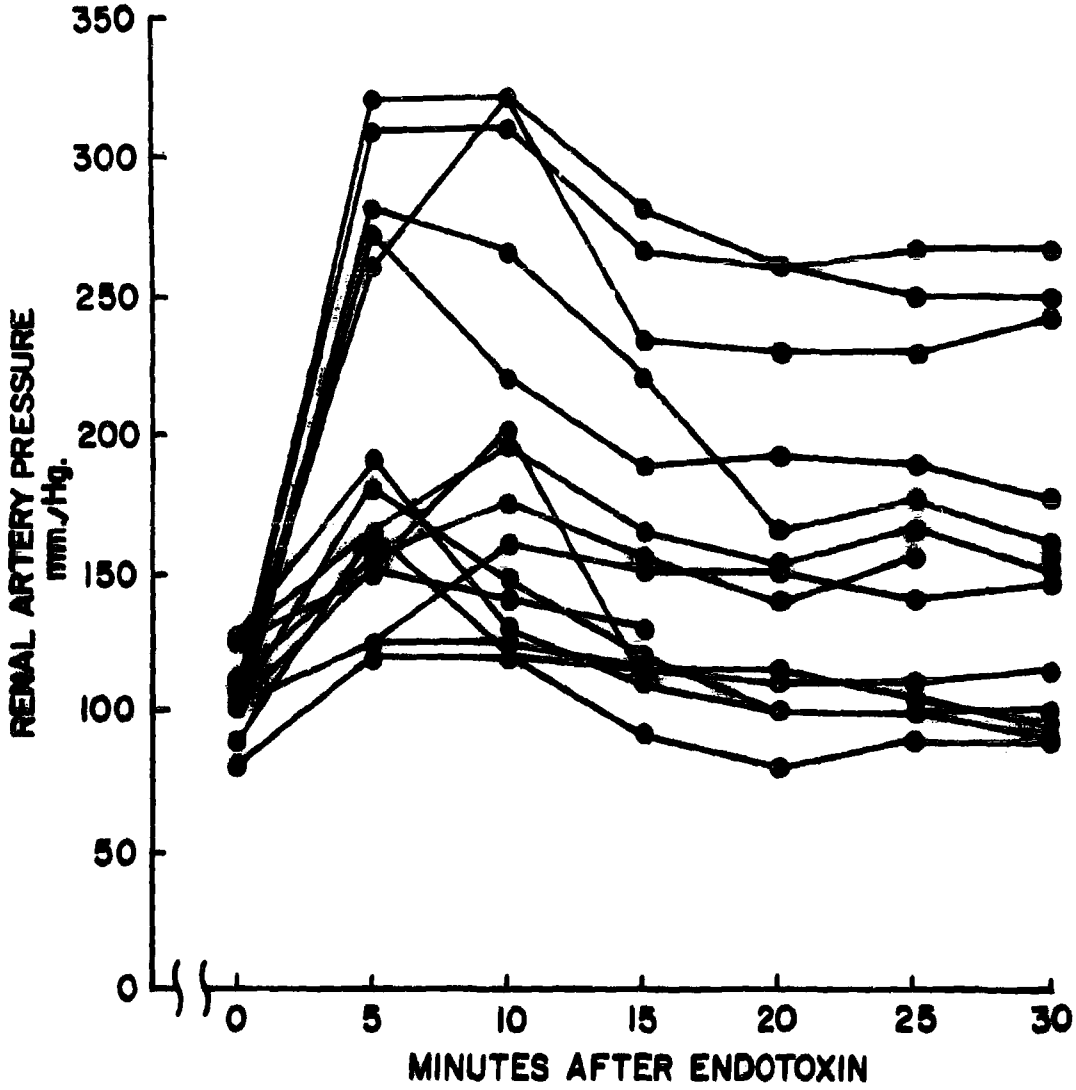

Fig. 3. The increase in renal arterial perfusion pressure of the 15 dogs given endotoxin locally into the renal artery.

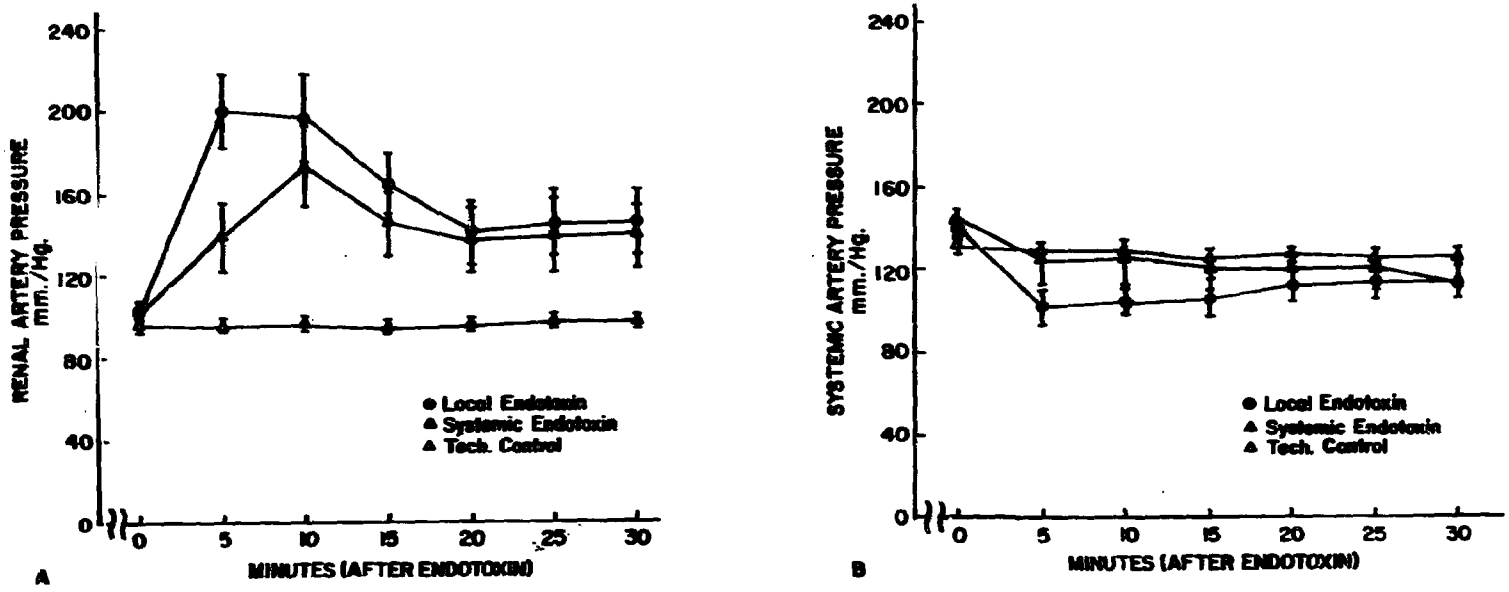

Fig. 4. Comparison of change in average renal arterial and systemic pressure after the local (15 dogs) and systemic (8 dogs) administration of endotoxin and the technique controls (5 dogs). ± 1 S.E.M. is indicated.

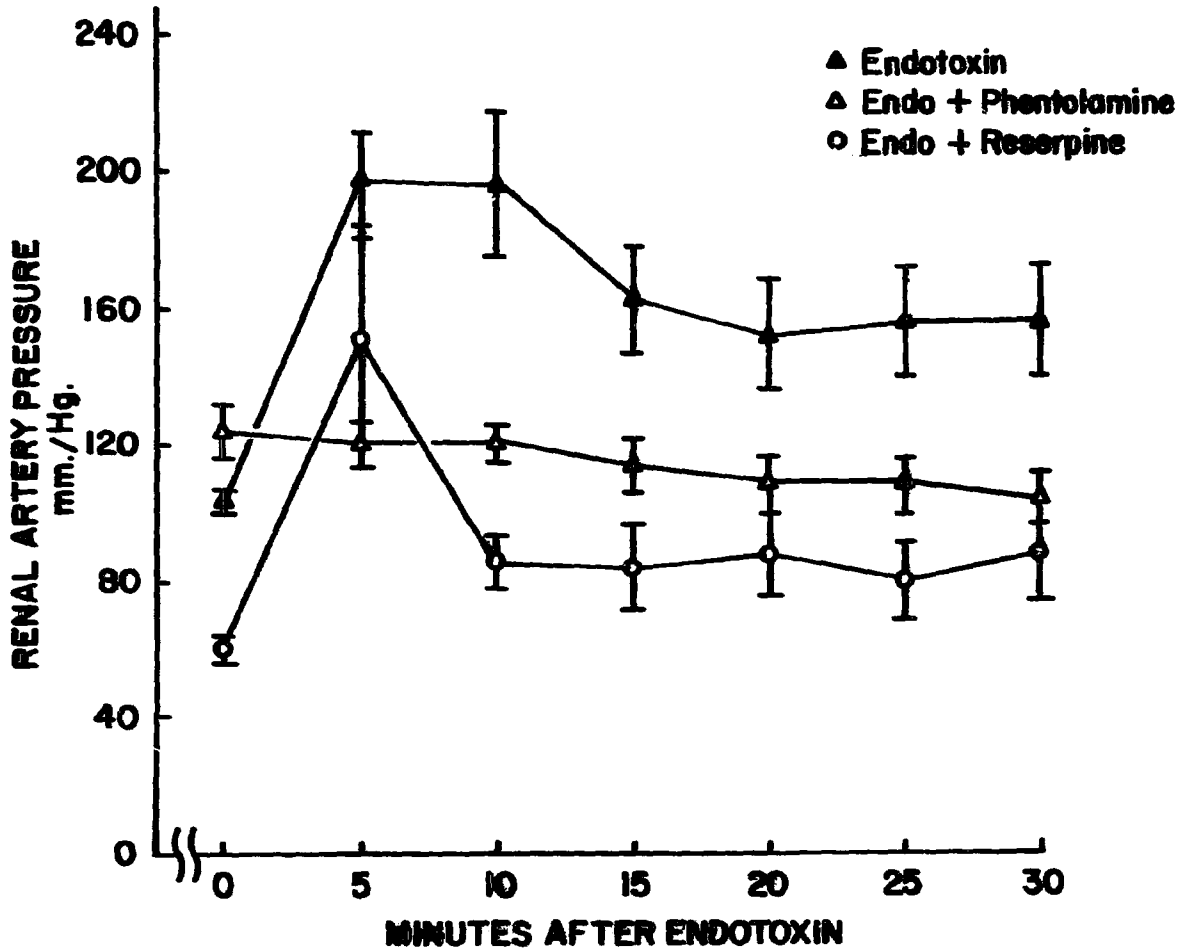

Fig. 5. Comparison of change in average renal arterial pressure after local endotoxin injection (15 dogs), local injection during phentolamine infusion (4 dogs), local injection in reserpinized animals (5 dogs). ± 1 S.E.M. is indicated.

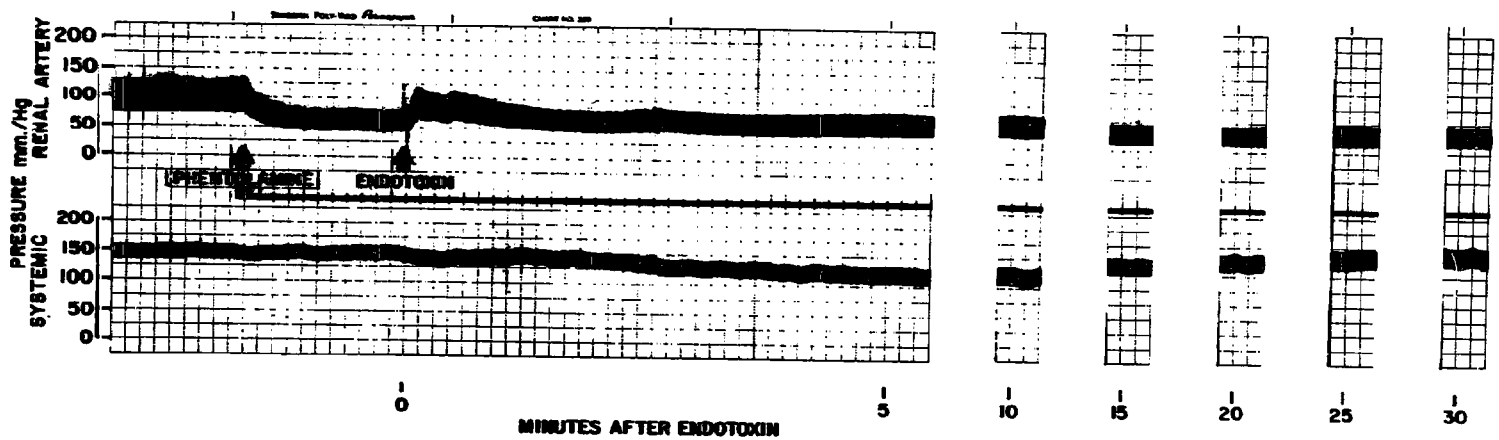

Fig. 6. A representative experiment in which endotoxin was injected into the renal artery during the local infusion of phentolamine. Note that there was still the initial transient vasoconstriction, but that the intense vasoconstriction usually seen at 5 to 10 minutes was blocked.

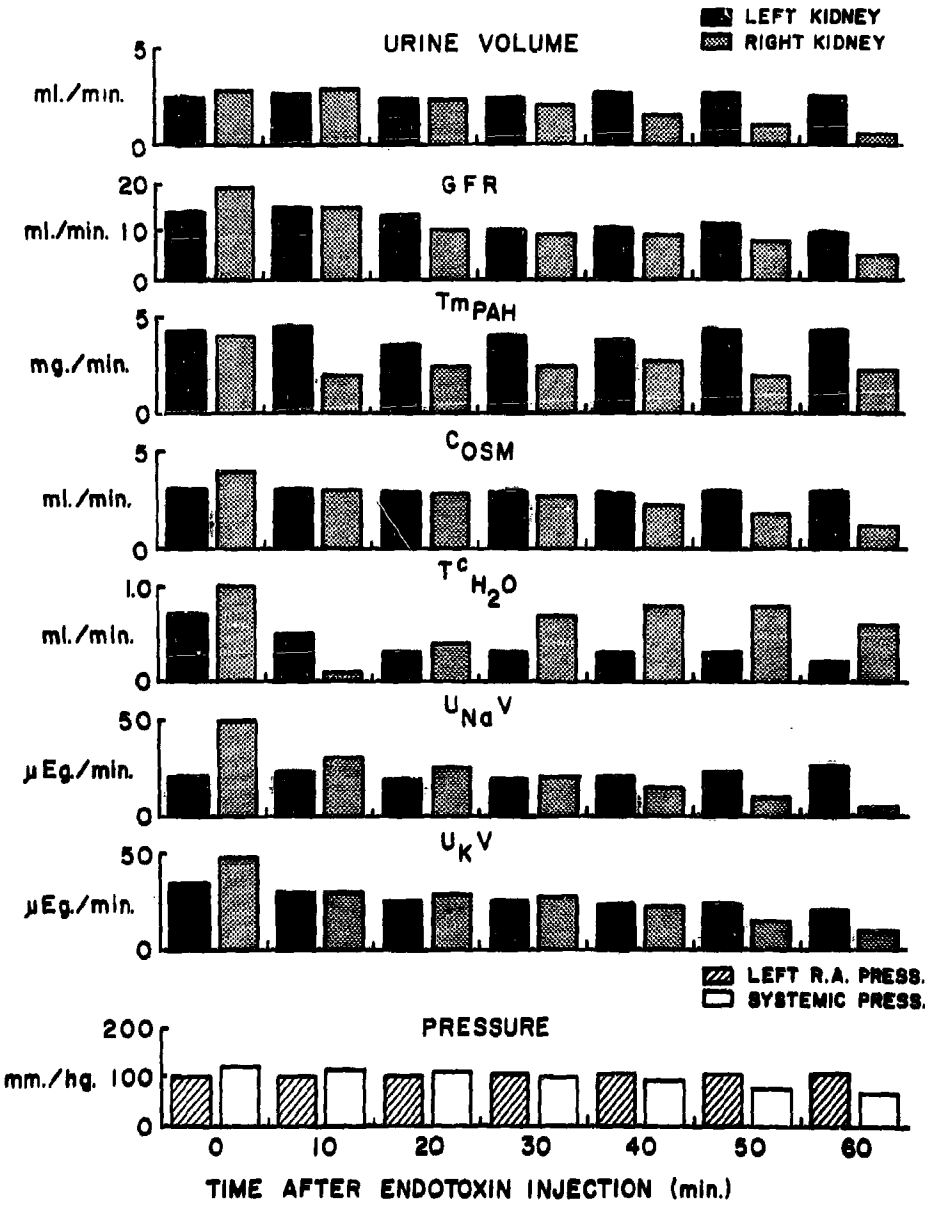

Fig. 7. Renal functions of a representative animal in which the hemodynamic effect was eliminated in the left kidney by infusing phentolamine locally and holding renal blood flow constant, enabling the comparison of this kidney with the contralateral undisturbed right kidney. In the left kidney in which vascular effects were eliminated there was no alteration in renal function.

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